In the Claims:

42. (Amended) An [ANT] isolated adenine nucleotide translocator polypeptide produced by [the] a method [of any one of claims 39-41] comprising culturing a host cell comprising a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the adenine nucleotide translocator polypeptide.

REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 42-57 are pending. Claim 42 has been amended to more clearly define the subject matter encompassed by applicants' invention, and to correct an improper dependency on non-elected claims. Support for the amendment may be found in the specification, for example, at page 6, line 29 through page 7, line 2; and claim 39. No new matter has been added.

The Examiner noted informalities with respect to the drawings. Applicants will attend to these informalities upon notification that the application is otherwise in condition for allowance.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 42-57 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not adequately described in the specification. More specifically, the Action asserts that the disclosure fails to provide a representative number of species to describe the genus of adenine nucleotide translocator (ANT) polypeptides or variants or fragments thereof. The Action alleges that the genus is highly variant because the specification and claims neither limit the number of structural differences between genus members nor indicate what distinguishing attributes are shared by the genus members. In addition, the Action asserts that the three species, ANT1, ANT2 and ANT3 alone are insufficient to describe the genus of ANT polypeptides or variants or fragments thereof.

Applicants respectfully traverse these grounds for rejection and submit that the description of the claimed invention in the specification is sufficient to reasonably convey to a person having ordinary skill in the art that the applicants, at the time of filing the application, had possession of the claimed invention. The present invention is directed in part to an isolated adenine nucleotide translocator polypeptide produced by a method of culturing a host cell having a recombinant expression construct that has at least one regulated promoter operably linked to a nucleic acid encoding the adenine nucleotide translocator polypeptide. The prior art and the instant specification teach that over 30 adenine nucleotide translocator polypeptides are known (29 complete and 3 incomplete sequences) from a variety of organisms, that several organisms encode two or three isoforms, and that the structure of this family of polypeptides is highly conserved (*see, e.g.*, specification, page 15, line 26 through page 16, line 2; and Fiore *et al.*, page 138, column 2 under "Genomic Structure of the ADP/ATP Carriers" and page 139, Figure 1 – cited in the Action). Further, there are a number of functional properties associated with adenine nucleotide translocator polypeptides (*e.g.*, specification at page 4, lines 5-22; page 13, line 27 through page 14, line 1; page 14, line 20 through page 15, line 3; page 39, line 12 through page 45, line 13; *see also* Fiore *et al.*, page 138, column 1, last paragraph). Thus, within the genus of adenine nucleotide translocator polypeptides, it is well established that there are a number of structural and functional properties that are shared among the species within the claimed genus. Accordingly, in view of the number of disclosed species of ANT polypeptides (*see, e.g.*, SEQ ID NOS:31-33), a person having ordinary skill in the art would recognize that applicants were in possession of the attributes common to the members of the genus.

Additionally, applicants respectfully submit that the instant specification conveys to a person having ordinary skill in the art that the applicants had, at the time of filing, possession of ANT polypeptides or variants or fragments thereof. As noted in the Action, the instant specification teaches that a "fragment" includes any ANT polypeptide that retains essentially the same biological function or activity as an ANT polypeptide (*e.g.*, specification, page 19, line 28 through page 20, line 3). Moreover, the biological functions or activities of ANT polypeptides or variants or fragments thereof are well known in the art, such as binding ligands (*see, e.g.*, specification, page 15, lines 1-6; and Fiore *et al.*, page page 138, column 1, last paragraph). Also, the instant specification teaches a person having ordinary skill in the art how to analyze

ANT polypeptides in structural and functional assays (*see, e.g.*, specification, Examples 10, 11, and 12) and the preferred degree of similarity or identity (*see, e.g.*, specification, page 20, line 20 through page 21, line 8). Thus, based on the instant specification, a person having ordinary skill in the art would readily recognize the claimed isolated ANT polypeptide, and could clearly determine the presence of a variant or fragment thereof.

Therefore, applicants respectfully submit that the instant specification and claims adequately describe the claimed invention and, consequently, that the present application satisfies the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, applicants respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 102(a)

(a) The Examiner rejected claims 42-46 under 35 U.S.C. § 102(a) as being anticipated by Marzo *et al.* (*Science 281*:2027-2031, 1998). More specifically, the Action asserts that Marzo *et al.* teach a purified human ANT2 protein. The Action further asserts that ANT2 is considered a variant of ANT1 and ANT3.

Applicants respectfully traverse this ground for rejection. Applicants submit that the cited reference fails to meet every limitation of the instant claims and, therefore, Marzo *et al.* fail to anticipate the claimed invention. As described in the specification and recited in the claims, the instant invention is directed in pertinent part to an isolated adenine nucleotide translocator polypeptide produced by a method of culturing a host cell having a recombinant expression construct that has at least one regulated promoter operably linked to a nucleic acid encoding the adenine nucleotide translocator polypeptide, and to an isolated human adenine nucleotide translocator polypeptide. Applicants respectfully submit that Marzo *et al.* fail to teach an isolated adenine nucleotide translocator produced recombinantly or a purified human ANT polypeptide. Indeed, Marzo *et al.* merely teach what was already known in the art, namely the purification of endogenous and naturally expressed ANT from rat myocardium (page 2029, column 1, lines 28-37; page 2030, Figure 4C). Marzo *et al.* fail, however, to teach an isolated ANT polypeptide produced by culturing a host cell having a *recombinant* expression construct comprising a *regulated* promoter operably linked to a nucleic acid encoding the ANT

polypeptide, as is provided by the present invention. Marzo et al. further fail to provide an isolated *human* ANT polypeptide.

Accordingly, applicants respectfully submit that the instant invention is readily distinguished over Marzo *et al.*, and request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

(b) The Examiner rejected claims 42-46 under 35 U.S.C. § 102(a) as being anticipated by Fiore *et al.* (*Biochimie 80*:137-150, 1998). More specifically, the Action asserts that Fiore *et al.* teach mitochondrial ADP/ATP carrier proteins (ANT proteins), providing evidence that ANT proteins are very well known in the art. In addition, the Action asserts that Fiore *et al.* disclose an amino acid sequence alignment of 29 sequences of known ANT proteins, particularly, human ANT1, ANT2 and ANT3 sequences.

Applicants respectfully traverse this ground for rejection and submit that Fiore *et al.* fail to anticipate the claimed invention because every limitation of the instant claims is not disclosed in the cited reference. In particular, applicants submit that Fiore *et al.* fail to teach an isolated ANT polypeptide produced by culturing a host cell having a *recombinant* expression construct comprising a *regulated* promoter operably linked to a nucleic acid encoding the ANT polypeptide. Fiore *et al.* also fail to teach an isolated *human* adenine nucleotide translocator polypeptide as disclosed in the present specification and recited in the instant claims. Applicants therefore submit that the Action does not point to any specific disclosure in the cited reference that anticipates any of the instant claims.

By contrast, applicants submit that Fiore *et al.* merely summarize conclusions drawn following the isolation of a beef heart adenine nucleotide translocator polypeptide, which is neither human nor the product of a cultured host cell comprising a recombinant expression construct according to the instant claims. The fact that isolated, non-recombinant beef heart ANT has been functionally characterized in no way anticipates the subject matter of the instant claims. Moreover, Fiore *et al.* teach that known ANT polypeptide *sequences* have been deduced from nucleotide sequences (page 138, column 2, lines 1-3 under "Genomic Structure of the ADP/ATP Carriers") without disclosing actual isolation of any human ANT polypeptides, nor of any ANT polypeptide produced by culturing a host cell comprising a recombinant expression

construct comprising a regulated promoter operably linked to an ANT-encoding nucleic acid. Applicants therefore submit that Fiore *et al.* fail to teach or suggest the subject matter of the instant claims.

Accordingly, applicants respectfully submit that the instant invention is readily distinguished over Fiore *et al.*, and request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(a)

(a) The Examiner rejected claims 43-57 under 35 U.S.C. § 103(a) as being unpatentable over Fiore *et al.* as applied to claims 42-46 above, and further in view of Rosenberg (*Protein Analysis and Purification: Benchtop Techniques*, Birkhäuser, Boston, pp. 335-347, 1996). More specifically, the Action asserts that it would have been obvious to express human and animal ANT protein sequences disclosed by Fiore *et al.* as fusion proteins according to the teachings of Rosenberg, wherein the fusion partner was a polypeptide or enzyme having affinity for a ligand to allow easier purification on an affinity column.

Applicants respectfully traverse this ground for rejection. The cited references, alone or in combination, fail to teach or suggest an isolated human adenine nucleotide translocator polypeptide, or an isolated human or animal adenine nucleotide translocator fusion protein comprising an adenine translocator polypeptide fused to at least one additional polypeptide sequence. As noted in the Action, Fiore *et al.* disclose a yeast strain containing an ANT carrying a polyhistidine tag at the C terminus, which was constructed to allow purification by immobilized metal ion affinity chromatography. Further according to the Action, however, Fiore *et al.* concededly fail to teach human or animal ANT fusion polypeptides. Applicants respectfully submit that Fiore *et al.* also fail to suggest human or animal ANT fusion polypeptides, that the Action has failed to point to any such suggestion in Fiore *et al.*, and that the state of the art therefore failed to contemplate how to achieve the present invention. Applicants further respectfully submit that, contrary to the Examiner's assertion, the addition of Rosenberg fails to remedy the deficiencies of Fiore *et al.* (which are also discussed above), and further that a person having ordinary skill in the art could not have reasonably expected to succeed in arriving at the claimed invention in view of the cited references.

Rosenberg is merely a general reference describing the construction and use of fusion proteins, including fusion proteins having an affinity tag and optionally a protease cleavage site to facilitate protein purification. Rosenberg fails, however, to provide any teaching or suggestion pertaining to the claimed isolated adenine nucleotide translocator polypeptides and fusion polypeptides. The teaching of Rosenberg, therefore, is merely cumulative subject matter. Applicants note, for example, that the instant specification discloses several fusion enzymes and affinity tag sequences that are known in the art (see, *e.g.*, specification page 21, line 20 through page 24, line 14; Examples 1, 2, and 3). Thus, the combined cited prior art does not render the claimed invention obvious. Rather, applicants submit that the Action employs impermissible hindsight to allege that the combined references would have motivated an ordinarily skilled artisan to arrive at the present invention.

Moreover, applicants submit that further evidence of the non-obviousness of the present invention is provided by the failure of the art to arrive at the claimed invention even where nucleotide coding sequences for human ANT were available as early as 1987 (see, *e.g.*, specification at page 15, lines 7-26), and where the art indicates a clear need for isolated ANT polypeptides according to the present invention (*e.g.*, Fiore et al. and references cited therein, describing ANT characterization using non-recombinant protein preparations). In this regard, applicants note that Fiore et al. also describe the versatility offered by recombinant yeast ANT fusions while remaining notably silent with regard to other sources of recombinant ANT, despite the availability of coding sequences for, *e.g.*, a variety of mammalian ANT polypeptides. As noted in the present application (*e.g.*, specification at page 4, lines 18-24; page 12, lines 16-23), prior to the present invention, certain inconvenient properties of the adenine nucleotide translocator appeared to preclude the availability of the presently claimed subject matter.

Applicants therefore respectfully submit that the Action has not set forth a *prima facie* case of obviousness. As discussed above, the cited references fail to provide a suggestion or motivation for a person having ordinary skill in the art to modify or combine the prior art teachings to arrive at the claimed invention with a reasonable expectation of success, and secondary considerations clearly show the invention to be non-obvious. Accordingly, applicants respectfully request that this rejection be withdrawn.

(b) The Examiner rejected claims 43-50 and 52-55 under 35 U.S.C. § 103(a) as being unpatentable over Adrian *et al.* (*Molecular and Cellular Biology* 6(2):626-634, 1986), in view of Fiore *et al.*, as applied to claims 42-46 above. More specifically, the Action asserts that it would have been obvious to substitute the human and animal ANT proteins taught by Fiore *et al.* with the yeast ANT in the fusion proteins taught by Adrian *et al.* In addition, the Action further asserts that one having ordinary skill in the art would have been motivated to make the above noted substitution to study the mitochondrial localization sequences of human and animal ANT as these proteins have a central role in cellular energy metabolism.

Applicants respectfully traverse this ground for rejection. The cited references, alone or in combination, fail to teach or suggest an isolated human adenine nucleotide translocator polypeptide, or an isolated human or animal adenine nucleotide translocator fusion protein comprising an adenine translocator polypeptide fused to at least one additional polypeptide sequence. The deficiencies of Fiore *et al.* have been discussed above and are further considered below. Adrian *et al.* merely teach the expression of fusion proteins consisting of *Saccharomyces cerevisiae* ADP/ATP translocator (ANT) proteins of various lengths fused to the enzyme β-galactosidase, in an investigation of which amino acids are important in targeting the protein to the mitchondrial membrane, as noted in the Action. Adrian *et al.* fail, however, to teach the subject invention human or animal ANT fusion proteins, as also acknowledged in the Action.

Nor, applicants submit, does the Action point to any suggestion in either Adrian *et al.* or in Fiore *et al.* to derive the ANT polypeptides and fusion proteins of the instant claims in a manner that would have motivated a person having ordinary skill in the art to believe these products could be obtained with a reasonable expectation of success. As also discussed above, the art was long aware of nucleic acid coding sequences for human and animal ANT polypeptides, and of general approaches to recombinant protein and fusion protein expression, yet the art had failed to overcome difficulties that are peculiar to ANT expression, prior to the present invention. Moreover, the disclosure of Adrian *et al.* is directed to a determination of whether yeast ANT shares mitochondrial targeting sequence motifs with other typical mitochondrial proteins, but Adrian *et al.* fail to contemplate in any way the expression of human or animal ANT polypeptides or fusion proteins.

Applicants submit that these deficiencies of Adrian *et al.* are not remedied by Fiore *et al.*, who, as noted above, merely disclose human and animal ANT polypeptide *sequences* deduced from nucleic acid coding sequences, but who fail to teach or suggest the actual *isolated polypeptides or proteins* of the instant claims. In particular, Fiore *et al.* are silent with regard to an isolated human ANT polypeptide, or to an isolated human or animal adenine nucleotide translocator fusion protein comprising an adenine translocator polypeptide fused to at least one additional polypeptide sequence. Additionally, applicants submit that the Action employs impermissible hindsight where it alleges that the claimed isolated human or animal adenine nucleotide translocator fusion protein is obvious solely on the basis of there being known to the art a yeast ANT fusion protein. On the contrary, applicants submit that Fiore *et al.* fail to teach or suggest to a person of ordinary skill in the art how to obtain an isolated human adenine nucleotide translocator polypeptide or an isolated human or animal adenine nucleotide translocator fusion protein. As noted in the instant specification, "those having ordinary skill in the art have heretofore been unable to produce ANT reliably or in sufficient quantities for a variety of uses, such as those provided herein" (*see, e.g.*, specification, page 4, lines 22-24), and applicants respectfully submit that the Action has failed to provide evidence to the contrary. Thus, absent the compositions and methods of the present invention, the cited prior art fails to provide the claimed subject matter to a person having ordinary skill in the art, with a reasonable expectation of success.

Accordingly, applicants submit that the Examiner has not met the initial burden of factually supporting a *prima facie* case of obviousness, and respectfully request that this rejection be withdrawn.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If the Examiner does not believe the claims are allowable for any reason, the Examiner is encouraged to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

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